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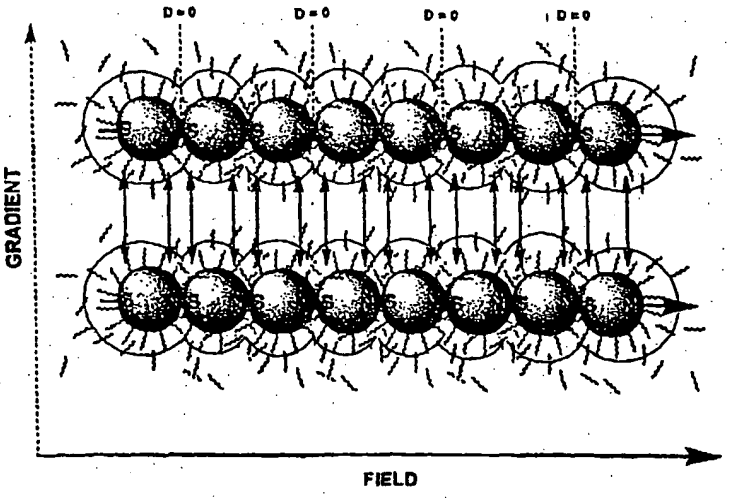
(54) Title: MAGNETICALLY RESPONSIVE EMBOLIC MATERIALS



(57) Abstract: An magnetically responsive embolic material includes coated magnetic particles comprising a core of one or more magnetic particles surrounded by a polymer coating. The particles can be disposed in a settable material, a biocompatible solvent, or a fluid carrier.

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MAGNETICALLY RESPONSIVE EMBOLIC MATERIALS

FIELD OF THE INVENTION

[0001] This invention relates to embolic materials, and in particular to magnetically responsive embolic materials for treating vascular defects.

BACKGROUND OF THE INVENTION

[0002] One method of treating vascular defects such as aneurysms is to create a blockage or embolism in the vasculature that isolates the defect. For example, a common treatment for aneurysms is to fill the aneurysm to remove the pressure from the aneurysm wall to prevent its continued expansion, and eventual rupture. This can be accomplished by introducing coils into the aneurysm which eventually cause a clot to form and fill the aneurysm. Several difficulties with these methods have limited their application. First, it is sometimes difficult to navigate a guide wire to the location of the vascular defect. Second, it is sometimes difficult to retain a catheter in place at the site of the defect. Third, in a wide-mouthed aneurysm, it can be difficult to place the coils entirely within the aneurysm, without protruding into the parent vessel, wholly or partially embolizing the parent vessel. Fourth, sometimes the aneurysm cannot be sufficiently filled to cause embolization, resulting in continued growth and possible rupture of the aneurysm. Although significant advances have been made in these procedures, as disclosed in co-pending U.S. Patent Application Serial No. 09/430,118, filed October 29, 1999, entitled Methods and Apparatus for Treating Vascular Defects, now U.S. Patent No. 6,375,606, the entire disclosure of which is incorporated herein by reference, additional methods of treating vascular defects are desirable.

[0003] More recently, efforts have been made to develop settable embolic materials that can be introduced into a vascular defect such as an aneurysm to occlude the defect. See, for example, U.S. Patent Nos. 6,037,366, and 5,695,480 incorporated herein by reference. However, it has proven difficult to accurately deliver settable embolic materials, and reliably retain them in place until they set. The process of injecting such materials is complex and difficult. The hemodynamic forces in the blood stream, combined with a lack of complete coherent stability within the embolic liquid, tend to slough off some of the embolic material and carry it into the healthy

vasculature. Efforts have been made to prevent this by putting a balloon or other containment element at the neck of the aneurysm, but this has proven difficult because such an element can be allowed to only briefly disrupt blood flow in the parent vessel, requiring precise control of filling and cure times. Consequently, only a very few, especially skilled interventional neuroradiologists have performed this liquid embolic filling procedure.

[0004] Some success has been achieved in adding magnetically responsive particles to embolic materials so that an externally applied magnetic field can be used to control the embolic material while it is being delivered to the site of the defect, and hold it in place while the material sets. See, for example, U.S. Patent No. 6,296,604, issued October 2, 2001, for Methods Of And Compositions For Treating Vascular Defects, the entire disclosure of which is incorporated herein by reference. However, careful control of the magnetic field and gradients was often required to prevent the material from clumping and/or forming dendritic structures that project from the defect site into the normal vasculature, and to prevent material from sloughing off into the blood stream and impairing the healthy vasculature.

[0005] A further complication of the magnetic control of embolic materials is the control magnet's interference with the imaging of the delivery of the embolic material. For example, Alksne et al. (J. of Neurosurgery 47: 137-141 (1977)), incorporated herein by reference, resorted to using a local magnet in the tip of a syringe delivered to the site of the aneurysm through a burr hole in the patient's skull. This tiny magnet apparently did not distort the image intensifier image, but required an invasive positioning of the magnet. Gaston et al., (J. Neuroradiology 15:137-147 (1988)), incorporated herein by reference, projected an image from a phosphorous plate across the room to an image intensifier far enough away from the magnet to avoid image distortion. However, this would obviously degrade image quality, and required the procedure to be performed in a darkened room.

[0006] While direct digital X-ray imaging plates would be substantially immune to the field of an embolic delivery magnet, at least some of the available digital x-ray imaging plates may not provide sufficient resolution for certain delicate neuro-vascular procedures such as aneurysm filling. The need for exquisite imaging detail is always present in the filling of an aneurysm, by any method, and highly evolved image intensifiers have been developed to provide this detail with the image

processing system of the fluoroscopes which image these procedures. These image intensifiers are large, and are sometimes close to the patient. They employ a method by which the ejected photoelectrons from the face of the image intensifier are guided to electronic cameras which amplify the intensity of the photon pattern on the tube face. As emitted the electrons have very low energy, and are vulnerable to distortion of their paths to the camera by even the low (~0.5 gauss) magnetic field of the Earth. Developments which reduce the Earth's magnetic effect are not able to the prevent problems with the hundreds, or even thousands of gauss fields of a nearby magnetic gradient source for embolic delivery. The size and magnetic strength of the source magnet needed to retain the embolic in the aneurysm before it is cured makes shielding difficult. As a result, one desirable feature of the embolic is that it be able to be aligned and pulled by the smallest fields and gradients possible.

[0007] The tendency of some prior magnetic embolic materials to clump and form dendrites resulted in the use of the transverse field of the magnet (where the field direction is perpendicular to the gradient direction) to control the direction of growth of these dendrites. The transverse field of a magnet is generally weaker than its axial field, so use of the transverse field requires larger magnets to achieve the same control, and this results in substantial axial fields that can interfere with even shielded image intensifiers.

SUMMARY OF THE INVENTION

[0008] The present invention employs materials and methods to improve the ability to quickly, easily, and safely treat vascular defects such as aneurysms. The embolic materials of the present invention include coated magnetic particles, either in a settable material, a biocompatible solvent, or a fluid carrier. As used herein a coated magnetic particle comprises one or more cores of a magnetically responsive material, with a coating of a non magnetic material partially or entirely surrounding the core(s). The coating may be filaments or hairs anchored to the magnetic cores and/or a continuous layer. The coated magnetic particles allow sufficient pulling force on the embolic to prevent hemodynamic disruption and sloughing of fragments from the main body of the embolic while at the same time leaving the embolic material which they comprise with a sufficiently low viscosity and short filling time for delivery through the small micro-catheters needed to deliver such material.

[0009] Generally, the coated magnetic particles comprise one or more cores of a magnetically responsive material of appropriate size to achieve strong response in an applied magnetic field and gradient. The core(s) is at least partially surrounded by a non-magnetic buffer coating to achieve a desired spacing of the magnetic material and the desired number density (and thus the density of magnetic material). The buffer coating may be a continuous layer or it may be discontinuous so long as it provides the desired separation of magnetic material. The buffer coating may allow for the inclusion of contrast materials so that the embolic material can be visualized with x-ray, fluoroscopic, MRI or other imaging methods. The buffer coating may also allow for cross-linking between the coated magnetic particles to enhance the properties of the embolic both prior to and subsequent to curing.

[0010] Through control of the size of the magnetic cores forming the coated magnetic particles, the thickness of the buffer coating, and the number density of the coated magnetic particles included in the embolic material, the tendency of the embolic material to slough off, and the tendency to form dendrites can be reduced. The reduction in the tendency to form dendrites allows the use of the relatively stronger end field of the control magnet, reducing the size of the control magnet needed, and reducing magnetic interference with other equipment image intensifiers, thereby allowing high-resolution imaging with only moderately shielded conventional image intensifiers. Through appropriate selection of the buffer coating, desirable properties such as cross-linking and radiopacity and MRI-opacity can be achieved.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Fig. 1A is a schematic drawing of a coated magnetic particle that might comprise a magnetic embolic material in accordance with the principles of the present invention;

[0012] Fig. 1B is a schematic drawing illustrating two coated magnetic particles in a transverse magnetic field, where the buffer coating is of sufficient size and strength to keep the coated magnetic particles in equilibrium;

[0013] Fig. 1C is a schematic drawing illustrating two coated magnetic particles in which the buffer coating is of insufficient size and strength to keep the coated magnetic particles in equilibrium, and thus the particles are irreversibly coagulated;

[0014] Fig. 2 is a drawing illustrating the repulsive forces between layered dipoles formed by agglomerated coated magnetic particles;

[0015] Fig. 3 is a graph of the Langevin function of degree of magnetic particle alignment plotted as a function of the magnetic particle size for a fluid of magnetite particles in a specified magnetic field;

[0016] Fig. 4 is a graph of some of the attractive and repulsive forces acting between adjacent magnetic particles as a function of particle surface-to-surface separation;

[0017] Fig. 5 is a graph of magnetic dipole pair interaction strength, showing the thermal equivalent effect of magnetic particle size on agglomeration rigidity;

[0018] Fig. 6 is a graph of the ratio of buffer coating thickness to magnetic particle radius needed to retain particle interaction at 14 kT strength;

[0019] Fig. 7 is a graph of the volume fraction of magnetite for a buffer to maintain a constant magnetic dipole strength at 14 kT;

[0020] Fig. 8 is a graph of the force on a 1 cc space for magnetically saturated magnetite in which the buffer is set for (a) constant dipole strength (14 kT) and (b) an *s/a* of 0.1;

[0021] Fig. 9 is a graph of the number of 1 eV bonds per square nm of particle surface which will equal the magnetic particle pair interaction energy as a function of particle radius;

[0022] Fig. 10 is a drawing of an alternate embodiment of the coated magnetic particle in which a plurality of magnetic particles or cores are embedded in a coating to form a single coated magnetic particle;

[0023] Fig. 11 is an NMR spectrum of the material of Example 2;

[0024] Fig. 12 is a photograph showing the clumping of magnetic particles in a magnetic field in a glass phantom;

[0025] Fig. 13 is a photograph showing the clumping of magnetic particles in a magnetic field in a glass phantom; and

[0026] Fig. 14 is a photograph showing the clumping of magnetic particles in a magnetic field in a glass phantom.

DETAILED DESCRIPTION OF THE INVENTION

[0027] This invention comprises an embolic material that includes coated magnetic particles. The coated magnetic particles can be disposed in a settable material, in a biocompatible solvent that acts on the coating, or in a fluid carrier such as water. The coated magnetic particles are magnetically responsive, and allow the embolic material in which the coated magnetic particles are disposed to be directed with an external magnet to the site of a vascular defect and held in place until set. The coated magnetic particles comprise one or more cores of a magnetically responsive material partially or completely surrounded by a non-magnetic buffer layer to separate the magnetic material.

[0028] According to a first aspect of this invention the coating thickness and the size of the magnetic cores are such that the attractive force between the coated magnetic particles in an applied magnetic field is attenuated sufficiently to reduce the undesirable clumping and dendrite formation while still in the fluid state. Bonding forces, either between the coatings on adjacent particles or between the coating of the particles and the embolic material in which they are disposed can help reduce undesirable clumping and dendrite formation of the coated magnetic particles.

[0029] According to a second aspect of this invention the coating allows various useful molecules to be attached to the coated magnetic particles. Thus molecules that form crosslinks may be bonded to the coating, so that the coated magnetic particles can be cross linked together. X-ray and/or MRI contrast agents also may be bonded to the coating to make the embolic material in which the particles are disposed "visible" to medical imaging equipment, so that the embolization procedure can be monitored.

[0030] In one preferred embodiment, the embolic material comprises coated magnetic particles in a settable material. The settable embolic material can be any suitable material with appropriate compatibility with the coated magnetic particles, biocompatibility, setting time, and durability. Examples of suitable materials include those disclosed in U.S. Patent No. 6,296,604, issued October 2, 2001, for Methods Of And Compositions For Treating Vascular Defects; U.S. Patent Application Serial No. U.S. Patent Application Serial No. 09/430,118, filed October 29, 1999, for Methods and Apparatus for Treating Vascular Defects; U.S. Patent Application No.

09/271,118, filed March 17, 1999, for Magnetic Vascular Defect Treatment System (now U.S. Patent No. 6,375,606); U.S. Patent Application No. 09/527,108, filed March 16, 2000, for Methods Of and Compositions For Treating Vascular Defects; and U.S. Patent Application Serial No. 09/790,219, filed February 21, 2001, New Embolic Compositions Including Prolamines, the disclosures of all of which are incorporated herein by reference, in their entireties.

[0031] In an alternative preferred embodiment, the embolic material comprises coated magnetic particles in a biocompatible solvent. The biocompatible solvent preferably partially dissolves or softens the coating on the particles. This facilitates mechanical and/or chemical interaction. As the solvent is removed from the embolic material after it is delivered to the vascular defect, for example by being absorbed in the blood stream, the coatings of the coated magnetic particles harden mechanically and/or by chemically bonding to form a cohesive embolism in the vascular defect.

[0032] In still another alternative embodiment, the embolic material comprises coated magnetic particles in a fluid carrier, such as water. The fluid carrier makes the coated magnetic particles more flowable, so that they are more cohesive and easier to control under the application of an external magnet.

[0033] In still another alternative embodiment, the embolic material will be stabilized against excessive agglomeration by repulsive long range screened Coulomb forces. With appropriate tuning, these can somewhat regulate the distribution of magnetic particles in the fluid embolic.

Magnetic Buffering

[0034] One aspect of the invention relates to buffering the magnetic attraction between the particles to reduce undesirable clumping and dendrite formation. The inventors have discovered that the greater the size of the magnetic particles in a magnetic embolic material, the greater the tendency of the magnetic particles to agglomerate in undesirable forms in an applied magnetic field, for example forming strings that mutually repel and thus can slough off, and/or form dendrites that extend beyond the defect and into the parent vasculature. Generally, the smaller the size of the magnetic particles, the less subject they are to agglomeration because of the disturbances from thermo molecular collisions with other particles, and thus the

greater the size of the magnetic particles, the more subject they are to agglomeration because they are less subject to these disturbances, which have a rotating, moment-reorienting effect. Generally, in the absence of a magnetic field, the smaller the magnetic particle size, the greater the viscosity of magnetic embolic material in which the particles are included because a greater number of particles is required to achieve a given magnetic responsiveness. This greater viscosity can interfere with the delivery of the embolic material through very small catheters into the vascular defects, because most of the material will not be in a strong magnetic field.

[0035] The inventors have further discovered that magnetic particle separation or spacing is also important to preventing the magnetic particles from permanently magnetically bonding as shown in Fig. 1C. By spacing the magnetic particles a minimum distance apart, the attractive force between the magnetic particles can be reduced, and thus the tendency of the magnetic particles to agglomerate in undesirable forms can be reduced. The inventors have discovered that minimum magnetic particle spacing can be controlled by using a buffer coating on the magnetic particles. Proper selection of the buffer coating thickness for the particular particle size helps control the attractive force between magnetic particles as shown in Fig. 1B, and prevents the magnetic particles from becoming permanently joined, as shown in Fig. 1C.

[0036] Magnetic particle density, that is the number of magnetic particles per unit volume, affects the responsiveness of the material to applied magnetic gradients. The greater the magnetic particle density (the magnetic material in a given volume), the greater the responsivity to a given gradient, or the smaller the gradient required to achieve a given pulling force. The viscosity of a magnetic embolic material increases with magnetic particle density. Thus magnetic particle density must be maintained high enough to make the material magnetically responsive, but low enough that the material has a workable viscosity. Magnetic particle density in turn is affected by coating thickness: the thicker the coating, the larger the size of the coated magnetic particle for a given amount of magnetic material, and the thinner the coating, the smaller the size of the coated magnetic particle for a given amount of magnetic material. Thus particle size, coating thickness, and particle density, are interrelated.

[0037] Larger magnetic core size is desirable to improve the magnetic responsiveness of the embolic material comprising the coated magnetic particles, but

larger magnetic cores also require thicker buffer coatings to prevent undesirable agglomeration. Smaller magnetic cores require a greater number density, which increases the viscosity of the embolic material containing the coated magnetic particles. Thicker coatings are desirable to reduce interparticle forces that cause undesirable agglomeration, but thicker coatings also increase particle size which reduces maximum particle density, and thus magnetic responsiveness.

[0038] An important aspect of a stable liquid embolic is the balance of interparticle forces of repulsion or disruption, magnetic and hemodynamic, and cohesive chemical forces which keep the material intact until cured. The magnetic repulsive forces arise when collective effects, the coagulation of groups of magnetic particles occurs, and one aspect of this invention is the management of these effects, among other ways by magnetic property choice, and by chemical buffering and bonding.

[0039] Agglomeration, the premature coagulating effect of magnetic particles, depends on a number of properties of the individual magnetic particles. Uniform spherical particles are discussed here, as a practical way of numerically assessing these properties, although it is known to those versed in the art how to calculate reasonable changes when particles are not all of the same size or shape. For present purposes, particle diameter of an inexactly spherical particle is taken to be the distance across the longest dimension, and the radius is one half of that distance.

[0040] The smallest practical particles, on the order of 10 nm diameter, form colloidal suspensions. That is, gravitational forces are not strong enough to force them out of suspension in a liquid. While magnetic forces are somewhat stronger, the principles are similar. The huge numbers of molecular collisions each second are randomizing in nature, and can cause reorienting effects as well as translational effects on the magnetic particles, of a strength dependent on the particles' masses, *i.e.* size. For particles of an effective size, the reorienting effects need not be complete, but can assist in reducing the strength of the agglomerating tendency, that is the collective increase of dipole lumps of particles which will repel other such lumps to the side, and for which the magnetic moment is parallel (not antiparallel). A well-known function, the Langevin Function, has been derived to show the fractional alignment of dipoles in a field, in the presence of these thermal randomizing collisions. With some discretion, the small particles can be treated as body-fixed

dipoles. Figure 3 shows this function for the case of a magnetic field aligning magnetite particles, as a function of their size. With no field, the particle individual magnetic moments are totally randomly directed, and show zero alignment. When uncoated magnetic particles are around 7 nm diameter, they are about 50% aligned. That is their statistically averaged moment projection on the magnetic field direction is about 50%. When uncoated magnetic particles are greater than 20 nm diameter, their alignment in the presence of thermal collisions is nearly, but not totally, complete. The effect of this degree of alignment is related to the tendency to agglomerate, and essentially to the functional dipole strength of the lumps of agglomerated material.

[0041] More specifically, the magnetic embolic material of the present invention consists of coated magnetic particles either in a settable embolic material and/or in a biocompatible solvent and/or a fluid carrier. The magnetic particles preferably comprise magnetic cores, preferably made of a permeable magnetic material, such as the iron oxides magnetite (Fe_3O_4) or maghemite (Fe_2O_3), or ferrites of the general form $MO\text{-}Fe_2O_3$, where M stands for Fe, Ni, Mn, Cu, or Mg. Most superparamagnetic, ferromagnetic, and ferrimagnetic metal alloys and garnets may also be used as magnetic bodies. Examples are Pt/Fe (ferromagnetic alloy) and $R_3Fe_5O_{12}$ (where R = atomic number 39, 62-71, ferromagnetic garnets). Cores of sub-micron size may be obtained through mechanical destructive methods such as ball milling and/or sonication. The cores preferably have an average diameter of between about 2 nm to about 1000 nm, and preferably between about 5 nm and about 500 nm. While it is preferred that the cores be roughly spherical, depending upon the method of production, the size and shape of the cores will vary.

[0042] The coated magnetic particles of the present invention have a buffer coating of a biocompatible material to maintain desirable magnetic core spacing and number density in the embolic material they comprise. Examples of suitable coating materials include: carbohydrates such as dextrans and starches, chitin, chitosan, carboxymethylchitosan, alginate, hyaluronic acid, polyacrylamides, polycyanoacrylates, hydroxyalkylpolycyanoacrylates, polyhydroxy acids such as polylactic acids, polyhydroxybutyrates, polyglycolic acids, polylactide-glycolides, polyorthoesters, polyanhydrides, polyurethanes, polyester imides, polyimides, polyacetals, poly-epsilon-caprolactones, polydioxanones, polyaminotriazoles,

poly(amideenamines), poly(amide-urethanes), polyphosphazenes, polyvinyl alcohols, organo-polysiloxanes, poly(enolketones), prolamines, proteins, polypeptides and copolymers of these materials, modified as necessary to introduce hydrophilic or lipophilic moieties. The coating can be up to the thickness of the diameter of the magnetic core, but is preferably between about 0.01 to about 0.2 times the diameter of the magnetic core, and more preferably between about 0.05 and about 0.1 times the diameter of the magnetic core. The thickness of the buffer coating is preferably selected so that the interparticle force in an applied magnetic field of at least 0.05 T does not exceed about 50 eV. Alternatively, or in addition, the thickness of the buffer coating is preferably selected so that the particle density is sufficient to provide a magnetic volume filling fraction (*i.e.* the volume fraction of a given volume of embolic material containing the coated magnetic particles that is a magnetic material) of at least about 10 percent, and preferably at least about 20 percent. Alternatively, or in addition, the thickness of the buffer coating is selected so that the embolic containing the coated magnetic particles has a magnetization in an applied magnetic field of 0.05 T or less of at least about 50,000 A/m, and more preferably at least about 100,000 A/m, and still more preferably at least about 200,000 A/m. Alternatively, or in addition the thickness of the buffer coating on the coated magnetic particles is such that the number density of the particles keeps the viscosity below about 2 poise and preferably below about 0.3 poise. Judicious selection of the size and density of coated magnetic particles aids in optimizing the design of the external magnet(s) that provide the magnetizing field and pulling gradient on the embolic. It is important that the embolic have high effective bulk magnetization, so that a smaller, weaker external (source) magnet can provide sufficient force. The reason for this is that a smaller source magnet interferes less, mechanically, with surrounding imaging equipment and its beams, and other medical equipment. The weaker magnet will interfere less, magnetically, with imaging and other equipment, and ease the shielding size, weight and expense. It is also important that the embolic be capable of being magnetized with relatively smaller magnetic fields, since that will ease the shielding issues of surrounding equipment. To this end, a good embolic could have effective pulling strength with a magnet having a high gradient-to-field ratio.

[0043] An initial difficulty of magnetic embolic materials that affects their ability to become stable liquids while filling an aneurysm is the tendency towards

agglomeration. This means that the small individual magnetic particles become dipoles when magnetized, which interact with each other. Figures 1and 2 illustrate this tendency when an external source magnet is used with its field perpendicular to its gradient, although the same tendency occurs when the fields and gradients are parallel. The magnetized dipoles individually attract each other when end-to-end, but repel each other when side-by-side, if aligned (magnetized) in the same direction (the field direction). This kind of instability forms dendrites as one consequence. These are the initial or primitive forms of agglomeration, which actually becomes a more irregular form of the same tendencies. In the case of perpendicular field and gradient, this means that long strings form of linearly attracting particles, but the strings repel each other.

[0044] Small magnetic particles can either be "single domain", or highly permeable as two extremes. A single domain particle will usually have its magnetization direction somewhat locked into a favorable geometric direction. This means that a long dimension will more likely be the direction of the internal magnetization, which will tend to align with the magnetic field. If a single domain particle is exactly spherical this will not be the case, but such a particle is an idealization. Nearly spherical particles will have the magnetization weakly coupled to the longer geometric direction. Highly permeable particles will have the magnetization along the field direction, but will tend to rotate so it is in the long geometrical direction. When clustered or agglomerated, such rotation is not easily possible, which can contribute to the irregularity of the clump forming.

[0045] The way that traditional ferrofluids have avoided the problem of agglomeration and also have a stable colloidal solution is to use magnetic particles so small that the thermal agitating forces help to prevent their nearly rigid "lock-step" alignment, at least partially. This occurs when the thermal energy 1/2 kT is roughly comparable to the interparticle "dipole-dipole" magnetic interaction energy, so that thermal motions are strong enough to randomize the orientation of the individual particles. This kind of analysis leads to the Langevin function which as discussed above is a measure of the fractional alignment of the particle magnetic dipoles along the source magnetic field direction as a function of the magnetic field applied. It is assumed for this that the magnetization direction within the particles is not easily changed, that is, the magnetization direction is either permanently fixed, or roughly

locked into a favorable geometric direction within the particle. Figure 3 shows the Langevin function plotted as a function of the particle size for a fluid of magnetite particles in a certain magnetic field, for idealized spherical particles. The magnetic moment of each particle is proportional to the cube of its diameter, and the magnetic aligning torque is proportional to this moment. Therefore the magnetic aligning torque increases rapidly with diameter.

[0046] The interaction strength between each pair of particles goes as the product of the moments. A coupling strength coefficient λ is given by a coupling coefficient,

$$\lambda = 0.5\text{x}(\text{dipole-dipole interaction energy})/(\text{thermal energyJ})$$

$$= K\, d^3/T$$

where d is the diameter, K a constant which contains the buffering ratio *s/a*, and T the absolute temperature (about 310 Kelvin). The coefficient λ measures the relative strength of interparticle magnetic interactions to the thermal agitation, and thus is somewhat related to the agglomeration tendency.

[0047] Two ideal spherical ferromagnetic particles, magnetized and touching each other end-to-end, would in principle, have an infinite force holding them together. It is almost impossible, however, for metallic particles to remain without some coating. This provides a natural buffer against such a strong and rigid interparticle force which would lead to agglomeration. Such a buffer, however, would usually be quite thin, and not very effective.

[0048] A typical chemical bond might be ~ 1 eV. To relate this to the scale of thermal energy, one eV is the energy of 37 kT_b, where T_b is the body temperature, about 37 degrees Celsius (310). In the figures an energy scale in units of kT is used to relate magnetic and thermal quantities with buffering, density, etc. This conversion factor can also relate effectiveness of chemical bonds to these issues. When magnetic particles or coated magnetic particles tend to align in an applied field as described previously, they tend to attract, end to end in strings as shown in Fig 2. Each such string will tend to repel a neighboring string, as also shown in Fig 2. Therefore, under most conditions it is important to provide a chemical coating of controlled thickness and with properties favorable to chemical adherence allowing some rotational freedom but not causing rigid attachments before curing. Such freedom would not be

expected if strong chemical bonds acted directly between each pair of particles. Such direct bonds would prevent any alignment of the magnetic particles, and therefore the gradient would not be effective in holding the embolic material in the aneurysm. Instead this selective freedom is to be accomplished by having (weaker) bonds acting between each particle and some other entity in the embolic which acts as a mediator until the curing is significantly completed. Such bonds might be weak chemical bonds, or some other microscopic physical bonding mechanism. The bonding of particles in syrup or other sticky fluids is an example.

[0049] There is another attractive force component that is effective at small separations between particles, the Van der Waal force. This must be considered when distances of a few nanometer are at issue. Fig. 4 illustrates several sources of potential energy between 10 nm spherical magnetite particles having steric repulsion (buffering) of several dimensions δ.

[0050] With the magnetic embolic materials of this invention, it can be useful to consider magnetite and other cores which are larger than 10 nm. These will have stronger interparticle magnetic forces and the buffering must be greater. The elements involved in providing optimization of the magnetic particle size and its buffering are shown in Figs. 5 through 8. Fig. 5, a plot of pair interaction strength versus diameters, illustrates on a log-log plot the rapid increase of interaction strength, in units of body-temperature thermal energy kT, between two fully magnetized magnetite spheres as their radii increase. It is seen that a 1 micron diameter magnetite particle pair will have 1,000,000 times the interaction strength of 10 nm spheres, assuming the particles are separated with a buffer layer of 10% of the particle radius. In particular, when the magnetic interaction energy is such a high multiple of kT the embolic will tend to rigidly clump and form dendrites (parallel field and gradient) or shear planes (field perpendicular to the gradient).

[0051] Fig. 6, a plot of buffer thickness versus particle radius, shows the buffer thickness s as a fraction or multiple of the radius a needed to maintain the magnetic interaction at 14 kT_b (the level where 10 nm particles exhibit colloidal behavior) as a function of magnetic particle radius. Particles of 100 nm radius would need a buffer thickness 19 times the particle radius. This is clearly impractical, and brings up another element in the optimization. The amount of magnetite in an embolic material containing such particles would be far too small to have the needed

pulling strength. A weak embolic such as this would be unable to overcome even gravity, let alone hemodynamic disruption. This is illustrated in Fig. 7, a plot of the magnetic volume fraction versus particle radius, where the packing of magnetite can be 40% of the volume for 10 nm magnetite particles buffered to keep the magnetic interaction at 14 kT. At the same condition, 100 nm particles would have only up to 0.0065 % of the volume. Fig. 8, a plot of bulk force versus particle radius, shows the force exerted on a one cubic centimeter sphere of fully magnetized magnetite as a function of particle radius. This assumes an embolic closely packed with the spheres, and a pulling gradient of 0.7 T/m. The two lines on the graph illustrate a constant buffer ratio of s/a = 0.1, and the buffer ratio found in Fig. 7 which was necessary to maintain the interaction energy at 14 kT.

[0052] Fig. 8 shows the impracticality of trying to keep the interaction strength down with large diameter magnetite particles by increasing the buffer coating thickness. As a force scale comparison, the weight of 1 cc of closely packed embolic is about 5 grams. A useful result of this, however, is that appropriate chemical or other bonding can permit the use of somewhat larger magnetic particles, *i.e.*, operation approximately along the line associated with $s/a = 0.1$, which will permit adequate magnetic volume fraction in the embolic.

[0053] The magnetic particle size issue is the question of an appropriate compromise, guided by these figures, and by chemical conditions discussed below. The most rigid of aggregations of the largest particles (*i.e.* greater than about 300 nm), only buffered by $s/a = 0.1$, will form dendrites or layers irrespective of any amount of cohesion that could be provided by polymers, in the liquid. A problem with the smallest of particles, ~10 nm, is that they will in a practical embolic result in a higher viscosity. It follows that highly concentrated (high-saturation-moment) embolic materials of greatest possible fluidity are favored by particles of small coating thickness s, large particle radius a, and spherical shape. These desired trends for s and a are opposite to the conditions favoring stabilization as a colloid, so in any actual ferrofluid compromises must be made using intermediate values of these parameters. An embolic need not be a ferrofluid, but it will suffer these same limitations. A ferrofluid is normally defined as a fluid containing small magnetic particles kept in (colloidal) suspension by thermal (Brownian) motion A significant difference in the

embolic is that a polymer is present, and (possibly) a separate contrast agent is present, and (possibly) separate cross-linking molecules are present.

[0054] In one embodiment, the embolic will use simple chemical bonding to resist agglomeration. In this case, a useful ratio of buffering to radius, *s/a*, can be approximately 0.1, with corresponding properties shown in some of the figures above. Chemical bonds, with an average strength of the order of 1 eV, acting on N bonds attached to the $4\pi(s+a)^2$ area of the particle on one end, and to some intermediate embolic entity, will resist the complete alignment and translational redistribution of magnetite particles of radius *a* which would give rise to serious agglomeration during the fluid phase. The pair interaction energy of $\pi\mu_o M^2 a^3/[9(s/a + 1)^3]$, converted to eV by multiplying by 1.6×10^{-19}, is used to find the total number of bonds of 1 eV strength needed to provide this resistance. This number, divided by the area, above, will yield the number of bonds per square nm needed to balance the magnetic energy (not necessarily exactly the quantity needed). This is plotted in Fig. 9 as a function of the particle radius. From a practical range of bond energy of 0.1 to 10 eV, this figure indicates that the balance is achieved for a range of bond density from roughly 4,000 nm^2 per bond to 40 nm^2 per bond, when the particle radius ranges from about 10 to 100 nm. In other words, very weak bonds could equal this energy. That would apply to several of the succeeding embodiments for stabilizing the embolic against separation, which could involve physical interactions not using chemical bonds.

[0055] The buffer coating can include cross-linking molecules that react to cross link the magnetic particles. The cross linking may be activated by electromagnetic radiation, *e.g.* ultraviolet radiation, infrared radiation, microwave radiation, gamma wave radiation, etc. The cross linking may alternatively be activated by contact with blood, solvent diffusion and/or polymerization initiators (anionic or radical). A choice among these methods depends on practical constraints, such as desired curing time or applicability to use in biological systems.

[0056] Diagnostic or therapeutic (*e.g.* pharmaceutical) agents may be bound to the buffer coating. Alternatively or additionally, cell adhesion promoters may be attached for therapeutic reasons.

[0057] A second embodiment of this invention might use a "softening" method against agglomeration. In one such method, metallic coating, or some other

means is used to provide like-charged magnetic (and coated) particles which repel each other with long-range electrostatic forces, and reduce the tendency toward agglomeration.

[0058] In a third embodiment of this invention, special bonds are arranged between particles. Bonds on particles along the intended field direction are made repulsive, weak, and long range, letting the magnetic aligning field provide the alignment. Bonds perpendicular to the field direction are made strong and attractive to offset the natural repulsion between strings of dipoles formed by the aligning field. Since filling methods may use either fields parallel to the attracting gradient (preferred) or perpendicular to it, these different bond arrangements can have some crystalline properties, chosen to be favorable to the particular form.

[0059] In a fourth embodiment of this invention, repulsive long-range screened Coulomb forces are used to combat the strong interparticle magnetic forces and reduce the agglomeration tendencies. Appropriately sized, these screened Coulomb forces can control the rigidity of the alignment without removing it significantly, so that the magnetic embolic can still be pulled strongly into the aneurysm by a reasonable gradient of an external magnet. A reference article, "A Model for the Yield Stress of Low Density Virus Solids," (R. Hastings, Physics Letters 67A, 316 (1978)), discusses the working of such repulsive forces in regularizing the distribution of 100 nm polystyrene spheres in aqueous suspension, and contains references to a number of studies of this type. A useful screened Coulomb potential $V = (Z^2e^2/r)e^{-2r/ro}$ has two parameters. These are 1) the charge Z, and 2) an average interparticle spacing $r_o \sim (N/V)^{-1/3}$, *i.e.*, the cube root of the number density. A charge $Z \sim 3{,}000$ and a screening length r_s of about 1/3 to 1/2 r_o was found effective for polystyrene spheres. Particle spacing control by the addition of such a screened potential can be seen for such a mechanism by one versed in the art. Limits to the effectiveness of this method with larger particles might come from the pH needed to maintain larger Z.

[0060] An alternative embodiment in which the core of the coated magnetic particle comprises a plurality of magnetic particles is shown in Fig. 10. In this alternative embodiment, the magnetic particles of between about 2 nm and about 300 nm in diameter, and preferably between about 5 nm and about 50 nm in diameter, are embedded in a coating material. The magnetic materials may be magnetite, the same

material forming the single particle core of the coated magnetic particles described above, or some other suitable magnetic material. The coating may be any of the coating materials described above. The resulting coated magnetic particles are between about 5 nm and about 1000 nm, and preferably between about 100 nm and about 300 nm.

Bonding Useful Molecules

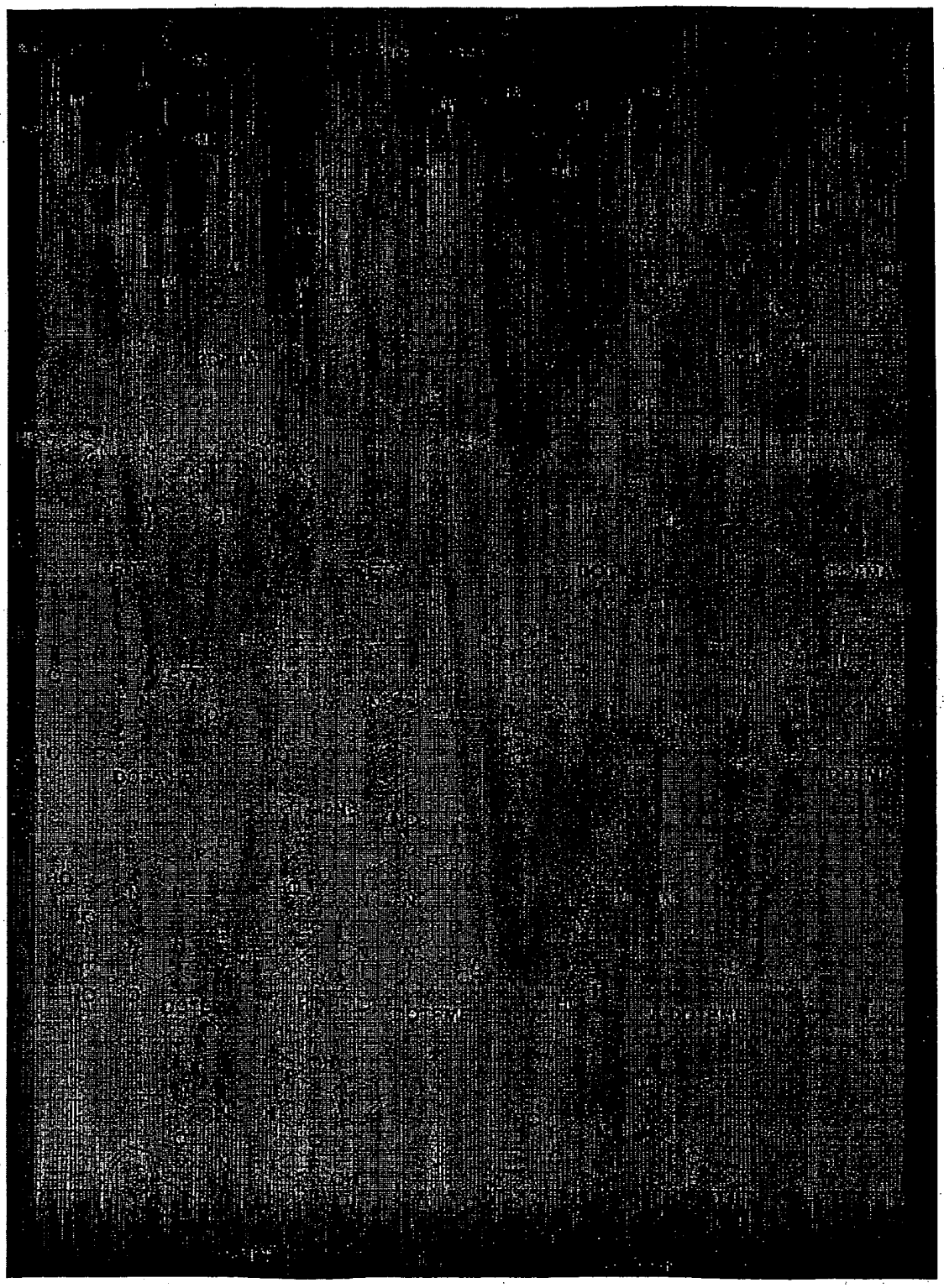
[0061] In addition to providing desirable separation or spacing of the magnetic particles comprising the coated magnetic particles, the buffer coating can allow other materials, such as cross-linking molecules and/or imaging contrast agents to facilitate visualization of the delivery of the embolic material into the vascular defect, to be included.

[0062] The buffer coating can allow particles to be cross-linked directly, or with the aid of cross-linking molecules provided for that purpose, to enhance the strength of the set embolic. These cross-linking molecules are preferably covalently bonded to the buffer coating. Suitable cross linking molecules include at least one of: epoxides, oxetanes, aziridines, oxazolines, isocyanates, activated alcohols, activated esters, activated amides, acrylates, cyanoacrylates, carbodiimides, glycolates, lactides, lactones, lactams, anhydrides, succinamides, hydrazides, aldehydes, amines, alcohols, thiols, oxalates, phthalimides, phthalates, spiro orthocabonates, coumarins and compounds containing any of theses groups.

[0063] The cross-linking reactions may be self initiating on exposure to blood as in the case of cyanocrylates, or a separate initiator can be provided. For example in the case of methylacrylate molecules, a peroxide may be provided as an initiator. For a free radical initiation, the radical produced may come from several different sources such as thermal decompositions of compounds with azo and peroxy groups, *e.g.*, benzoyl peroxide and "redox reactions", *e.g.*, Bimolecular initiating systems Fe^{2+}/persulfate, Co^{2+}/tert-Butyl hydroperoxide or peroxydisulfate. Radical initiation may also come from various photochemical-induced decompositions, *e.g.*, peroxides, azo compounds, disulfides, ketones and aldehydes and also ionizing radiation, *e.g.*, Strong gamma sources ^{60}Co or ^{90}Sr. Various retardants and controls can also be provided to control the rate of the reaction, and thus the setting time.

[0064] Imaging contrast agents, *e.g.*, radiopaque materials, to facilitate visualization of the embolization process, can be included. Suitable x-ray contrast agents can include at least one of mono-, di-, or tri-iodinated benzoic acid and derivatives, iodinated aniline/isophthalmic acid derivatives (*e.g.*, metrizamide, iopamidol, iomeprol, iopromide, ioversol, iohexol, iopentol, ioxilan, iogulamide, ioglucol), ioglucamide, ioglunide, iosimide, iocibidol, iofratol, iodixanol, iotrol, iotrasul, iodecol).

[0065] Alternatively, or in addition, MRI contrast agents can also be included. The MRI contrast agent can include at least one of: EDTA, DPTA, DOTA, TRITA, TETA, DOTA-MA, DO3A-HP, DOTMA, DOTA-pNB, DOTP, DOTMP, DOTEP, DOTPME, F-DOTPME, DOTPP. DOTBzP with possible covalently bound side chain comprising of 1-hydroxy-2-pyridones, 3-hydroxy-2-pyridones, 3-hydroxy-4-pyridones, hydroxymates, catechols, tropolones, amino acids, aminophosphi(o)nic acids, aminophenols, quinolines, 3-pyridine-carboxylic acids, imidazole-carboxylic acids, aminothiols, amidethiols, diamines and peptides/proteins with a preferred chelated bi- or tri- metal comprising of chromium(III), manganese (II), iron(II), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III) but not excluding any other element.

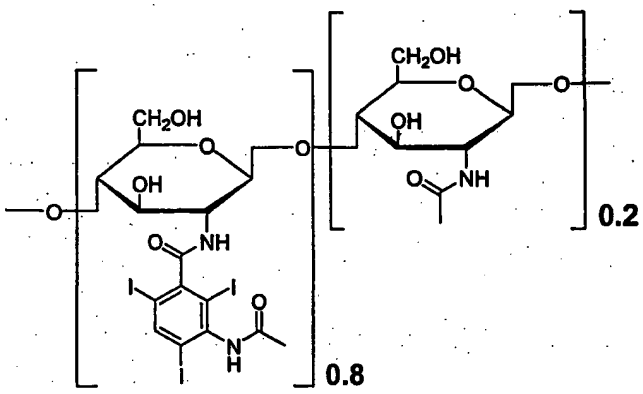


Example 1

[0066] The following example illustrates the preparation of a radiopaque polymer with internal crosslinker (Modified procedure of Nishimura et. al Macromolecules, 1991, 24, 4645-4748, incorporated herein by reference). The radiopaque chitosan derivative was suspended in anhydrous pyridine (20 mL) at 60oC. Methacryloyl chloride (0.58 mL) was added dropwise and the mixture was allowed to stir for 48 hr at 60oC closed to light. The thick mixture was then added dropwise to vigorously stirred acetone upon which a colorless precipitate formed which was then collected by filtration. The solid was then purified by Soxhlet extraction with ethanol for 24 hr, dried under vacuum to give 0.649g pale yellow solid.

Example 2

[0067] The following Example demonstrates the ability to make coated magnetic particles radiopaque. Chitosan (Vanson 80% deacetylated) was suspended in demineralised H_2O (2.5 g) under Argon and pH was adjusted to 6 by addition of concentrated HCl dropwise upon which the solid dissolved. 3-Acetamido-2,4,6-triiodobenzoic acid (8.54 g) in demineralised H_2O (90 mL) under Argon was adjusted to pH 6 with 1N NaOH. The two solutions were combined and EDC.HCl (2.94g) was added and the pH checked again to maintain in at 6. After stirring for 3 days at room temperature the solution was subjected to exhaustive dialysis with demineralised H_2O, then 0.1N NaOH and again with demineralised H_2O. The product was precipitated by pouring dropwise into rapidly stirred acetone (300 mL) and the resulting white precipitate was filtered washed with MeOH (500 mL), Et_2O (500 mL), air dried and then lyophillisded for 24 hours to give 3.624 g colourless solid. The structure is shown as follows:



The NMR spectra is shown in Fig. 11.

Signal δ (ppm)	Inference
1.97	CH_3CONH (0.2)
2.16	CH_3CONH-Ar (0.8)
2.81	C(2)-H (0.2)
3.04	C(2)-H (0.8)
3.65	C(6)-H
3.79	C(1)-H
8.37	Ar-H

Example 3

[0068] The follow example demonstrates the performance of uncoated micron-sized magnetite particles. A solution of 0.5 gm of magnetite (Pea Ridge Company, Sullivan, Missouri, USA), particle size approximately 1-10 microns, in 2 ml of deionized water was injected into an aneurysm flow phantom using a 150 cm length fabricated microcatheter (0.022" ID Marlex tube with Leur Lock connector). The flow phantom consisted of a polyurethane lateral aneurysm model connected to a pump flow system. The lateral aneurysm model had a lumen with a 4 mm vessel and a 7 mm diameter lateral aneurysm. The model was filled with a static fluid containing a mixture of one part saline to two parts glycerol, to mimic the viscosity of blood. A permanent magnet was placed a distance of one inch from the neck of the aneurysm, providing an axial field of 0.10 T and a gradient of 3.9 T/m. During the fill, dendrite formation began immediately and was severe, resulting in a fill with a very ragged boundary at the interface between mimicking fluid and sample material (see Figure 12). The final fill exhibited significant striations.

Example 4

[0069] The following example demonstrates the performance of uncoated nanometer-sized particles. A solution of magnetite (EMG 1111, Ferrotec, Nashua, New Hampshire, USA), particle size approximately 10 nanometers, in water was injected into an aneurysm flow phantom with external magnet as described in Example 3. During the fill, dendrite formation began immediately and resulted in a fill with a ragged boundary at the interface between mimicking fluid and sample material (see Figure 13). The final fill exhibited moderate striations.

Example 5

[0070] The following example demonstrates the performance of chitosan-coated nanometer sized particles. Chitosan-coated magnetite material was prepared by suspending 2 gm of chitosan in 50 ml H^2O and adding concentrated glacial acetic dropwise until a thick solution was formed. Then, 1 gm of Fe_3O_4 (10 nm average diameter, Ferrotec, Nashua, New Hampshire, USA) was added and the solution was degassed with an ultrasound bath for 30 minutes at 60°C under an argon atmosphere. 0.1 mL Triton X-100 was added to reduce surface tension within the mixture. The chitosan magnetite mixture was then added dropwise to a degassed NaOH solution (40g NaOH in 250 ml H_2O) over a period of 30 minutes while stirring with an overhead stirrer at 1000 rpm. A black precipitate formed instantly on addition to the basic solution which was then further stirred at 500 rpm for 1 hour at 80°C. The coated magnetite was then magnetically collected and the supernatant discarded. The material was then taken back up in deionized water and collected again magnetically and the supernatant was discarded. This procedure was repeated until washings were pH neutral. The black/brown material remaining was filtered using a medium fritted funnel and washed with copious amounts of H^2O, then acetone, and then diethyl ether. Finally, the solid was lyophilized overnight to remove residual H^2O. The collected material showed a 10 nm diameter Fe_3O_4 cores with ?? nm diameter overall particle size by TEM.

[0071] A solution of the chitosan-coated magnetite in water was injected into an aneurysm flow phantom with external magnet as described in Example 3 except that pulsatile flow was established at 120 mL/min. During the fill, no dendrite

formation was observed. The resulting fill was very smooth and even (see Figure 14). The final fill exhibited no striations.

What is claimed is:

1. A magnetically guidable embolic comprising a plurality of coated magnetic particles each comprising at least one core of a magnetically responsive material at least partially surrounded by a non magnetically responsive coating.

2. The magnetically guidable embolic according to claim 1 wherein the cores of magnetically responsive material have an average diameter of between about 5 nm and about 1000 nm.

3. The magnetically guidable embolic according to claim 2 wherein the cores of magnetically responsive material have an average diameter of between about 4 nm and about 500 nm.

4. The magnetically guidable embolic according to claim 3 wherein the thickness of the coating is between about 0.01 and about 0.25 of the diameter of the core.

5. The magnetically guidable embolic according to claim 4 wherein the thickness of the coating is between about 0.01 and about 0.10 of the diameter of the core.

6. The magnetically guidable embolic according to claim 5 wherein the coating has a thickness of between about 0.02 and about 0.07 of the diameter of the core.

7. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles are disposed in a settable material.

8. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles are disposed in a biocompatible solvent.

9. The magnetically guidable embolic according to claim 8 wherein the coated magnetic particles are disposed in a biocompatible solvent which softens the non-magnetically responsive coating, and which upon deposition of the embolic material in a subject's body is absorbed by the patient's blood, causing the coating to harden.

10. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles are disposed in a fluid carrier.

11. The magnetically guidable embolic according to claim 1 wherein there are between about 4 x 10^{13} and about 2 x 10^{20} coated magnetic particles per milliliter.

12. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles comprise between about 10 and 60 percent of the volume of the material in liquid form.

13. The magnetically guidable embolic according to claim 1 wherein magnetically responsive material comprises between about 1 and about 25 percent of the volume of the embolic.

14. The magnetically guidable embolic according to claim 13 wherein magnetically responsive material comprises between about 1 and about 5 percent of the volume of the embolic.

15. The magnetically guidable embolic according to claim 13 wherein magnetically responsive material comprises between about 1 and about 3 percent of the volume of the embolic.

16. The magnetically guidable embolic according to claim 1 wherein the total magnetic force on a 1 cm^3 of the embolic is between 1 and 5 times the weight of the material when the embolic is in a magnetic gradient of 0.7 T/m.

17. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles include cross linking molecules covalently bonded to the coating, which cross linking molecules react upon deposition of the embolic in a subject's body to form crosslinks between the coated magnetic particles.

18. The magnetically guidable embolic material according to claim 17 wherein the cross linking molecules comprise at least one of: epoxides, aziridines, oxazolines, isocyanates, activated alcohols, activated esters, activated amides, acrylates, cyanoacrylates, carbodiimides, lactones, lactams, anhydrides, succinamides, hydrazides, aldehydess, amines, alcohols, thiols, phthalimides, coumarins and compounds containing any of theses groups.

19. The magnetically guidable embolic according to claim 17 further comprising a retardant for controlling the reaction rate of the cross linking molecules.

20. The magnetically guidable embolic according to claim 19 wherein the retardant comprises at least one of hydroxyquinone, p-methoxyphenol, inorganic

acids (e.g., phosphoric acid), carboxylic acids (e.g. glacial acetic acid), organic sulfides, organic sulfates, organic sulfides, organic sulfones, organic sulfoxides, mercaptans, cyclodextrins and/or compounds containing these groups.

21. The magnetically guidable embolic according to claim 17 wherein the cross linking molecules comprise cyanoacrylate.

22. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles include an x-ray contrast agent covalently bonded to the polymer layer.

23. The magnetically guidable embolic according to claim 20 wherein the x-ray contrast agent comprises at least one of: mono- di- or tri-iodinated benzoic acid and derivatives, iodinated aniline/isophthalmic acid derivatives (including metrizamide, iopamidol, iomeprol, iopromide, ioversol, iohexol, iopentol, ioxilan, iogulamide, ioglucol), ioglucamide, ioglunide, iosimide, iocibidol, iofratol, iodixanol, iotrol, iotrasul, iodecol.

24. The magnetically guidable embolic according to claim 1 wherein the coated magnetic particles include an MRI contrast agent covalently bonded to the coating.

25. The magnetically guidable embolic according to claim 22 wherein the MRI contrast agent comprises at least one of: EDTA, DPTA, DOTA, TRITA, TETA, DOTA-MA, DO3A-HP, DOTMA, DOTA-pNB, DOTP, DOTMP, DOTEP, DOTPME, F-DOTPME, DOTPP. DOTBzP with possible covalently bound side chain comprising of 1-hydroxy-2-pyridones, 3-hydroxy-2-pyridones, 3-hydroxy-4-pyridones, hydroxymates, catechols, tropolones, amino acids, aminophosphi(o)nic acids, aminophenols, quinolines, 3-pyridine-carboxylic acids, imidazole-carboxylic acids, aminothiols, amidethiols, diamines and peptides/proteins with a preferred chelated bi- or tri- metal comprising of chromium(III), manganese (II), iron(II), iron (III), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III) or erbium (III).

26. The magnetically guidable embolic according to claim 1 wherein the coating comprises at least one of a polysaccharide and a polyaminoacid.

27. The magnetically guidable embolic according to claim 26 wherein the coating comprises a chitosan polymer.

28. The magnetically guidable embolic according to claim 17 wherein the cross-linking is activated by electromagnetic radiation.

29. The magnetically guidable embolic according to claim 17 wherein the cross-linking is activated by ultrasound.

30. The magnetically guidable embolic according to claim 17 wherein the cross-linking is activated by contact with blood, solvent diffusion and/or polymerization initiators (anionic or radical).

31. The magnetically guidable embolic according to claim 1 further comprising a therapeutic agent covalently bonded to the coating.

32. A magnetically guidable embolic including coated magnetic particles comprising magnetic bodies with a buffer coating, in which the buffer coating is between about 5% and about 20% of the diameter of the magnetic bodies.

33. A magnetically guidable embolic including coated magnetic particles comprising magnetic bodies with a buffer coating, in which the average size of the bodies and the thickness of the buffer coating have a ratio between 3 to 1 and 30 to 1.

34. A magnetically guidable embolic including coated magnetic particles comprising magnetic bodies with a buffer coating, in which the average size of the bodies and the thickness of the buffer coating have a ratio of 10 to 1.

35. The magnetically guidable embolic according to claim 34 wherein the material has a pulling force of at least 2 grams per cubic centimeter in a gradient of 0.7 T/m.

36. A system for delivering a magnetic liquid embolic to a vascular defect in a subject consisting of: a magnetically shielded X-ray image intensifier, a liquid embolic delivered to the site of the vascular defect through a catheter, and a magnet external to the subject which uses the axial magnetic field of the magnet, with the magnetic field parallel to the magnetic gradient at the site of the defect, to control and hold the liquid embolic within the defect during delivery.

37. A magnetically navigable embolic material comprising a settable material including coated magnetically responsive cores which provide a sufficient volume of magnetic material to be magnetically attracted by the gradient of an external magnet, and in which the coating produces a combination of separation of

repulsive forces between cores and attraction between coatings sufficient to reduce sloughing of the materials in hemodynamic forces.

38. A magnetically assisted method of embolizing a vascular defect comprising applying a magnetic gradient generally perpendicular to the plane of the mouth of the aneurysm; introducing a settable embolic material into the mouth of the aneurysm, the embolic material including coated magnetically responsive particles having cores of a magnetically responsive material of sufficient volume that the applied gradient can hold the material in the aneurysm and the coating providing sufficient spacing to reduce interparticle repulsive forces sufficient attachment between particles to prevent hemodynamic forces from sloughing material from the defect.

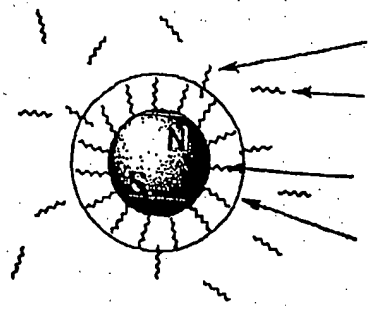


Fig. 1A

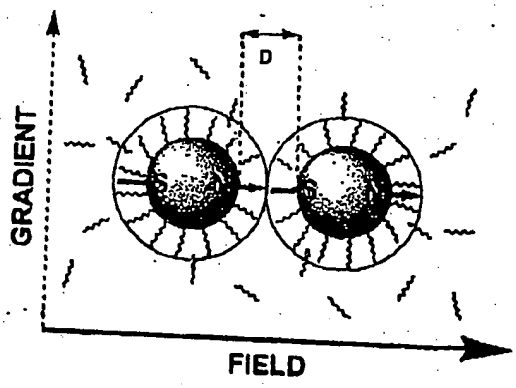


Fig. 1B

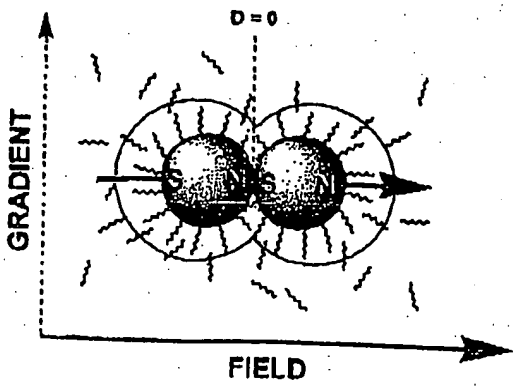
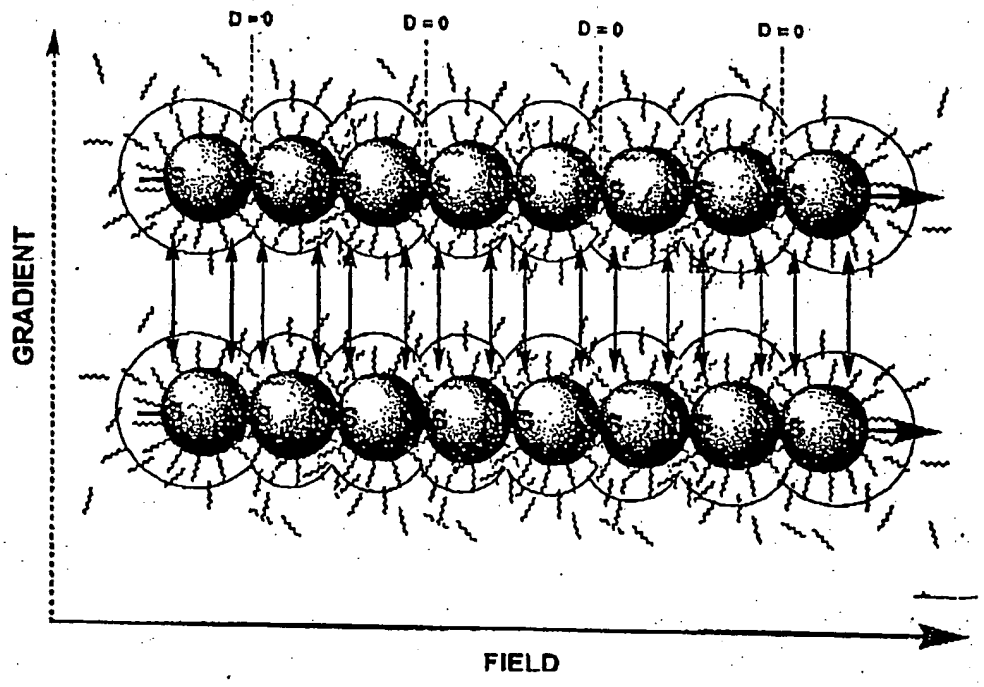


Fig. 1C


D=0
D=0
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GRADIENT
FIELD
REPULSIVE FORCES BETWEEN
LAYERED DIPOLES

Fig. 2

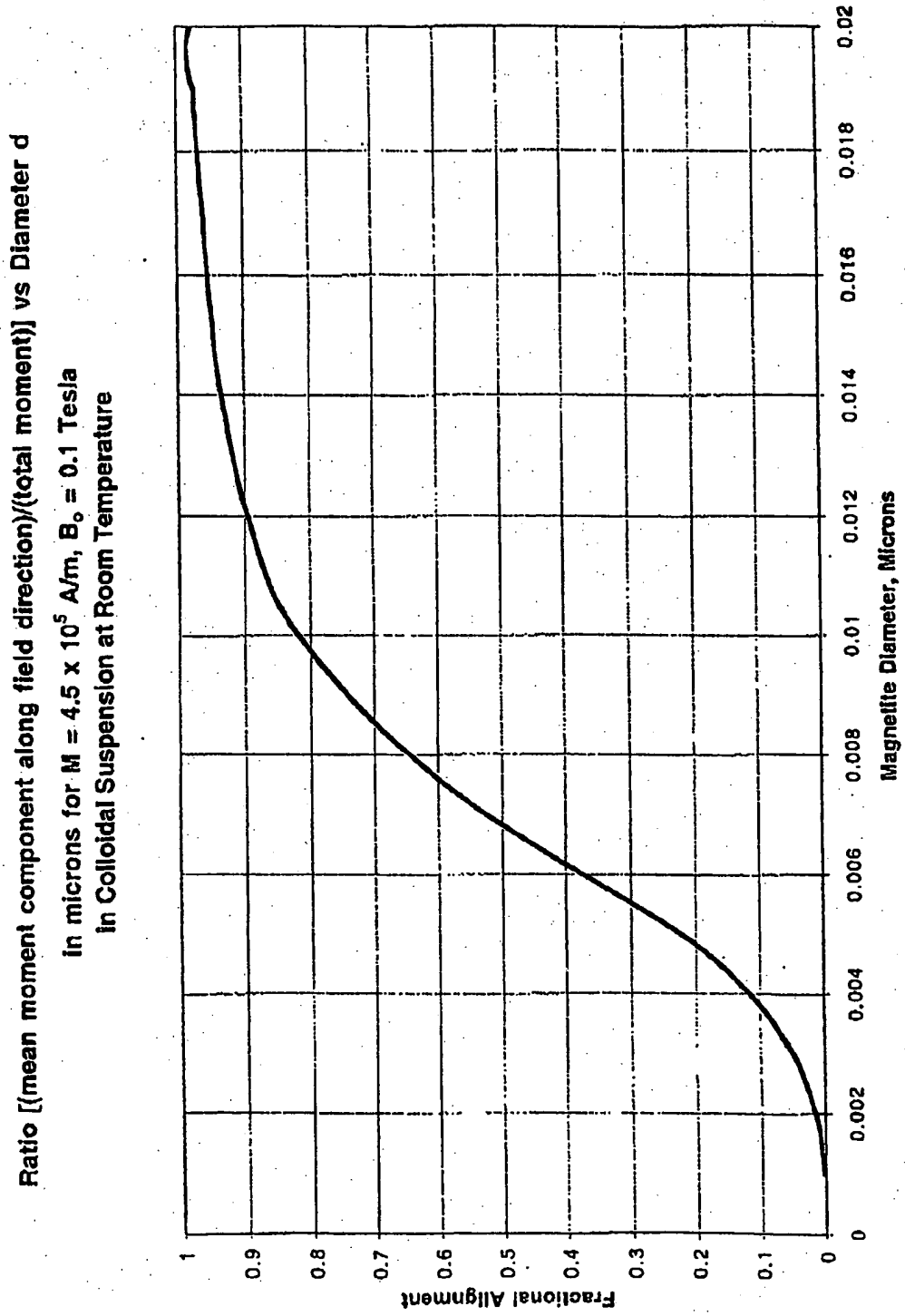
Ratio [(mean moment component along field direction)/(total moment)] vs Diameter d
in microns for M = 4.5 x 10^5 A/m, B_o = 0.1 Tesla
in Colloidal Suspension at Room Temperature
Fractional Alignment
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.002
0.004
0.006
0.008
0.01
0.012
0.014
0.016
0.018
0.02
Magnetite Diameter, Microns

Fig. 3

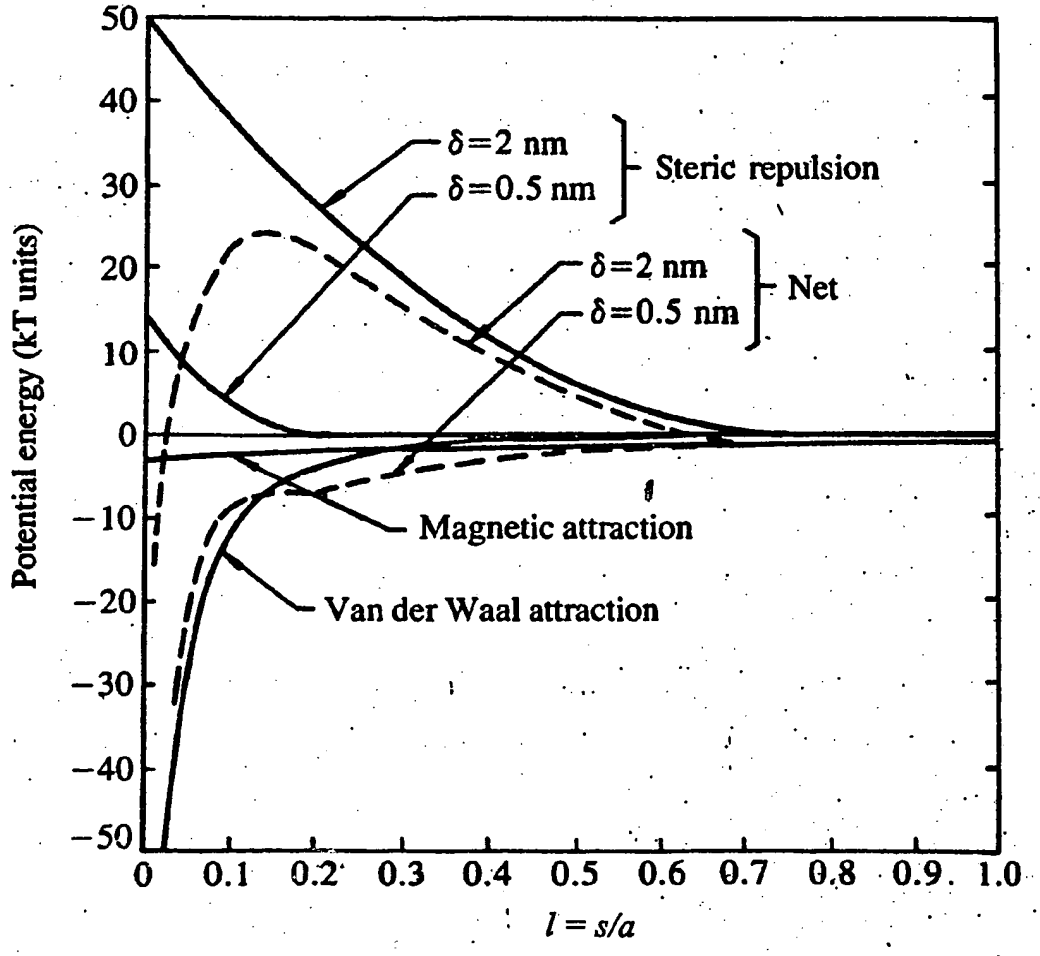
50
40
30
20
10
0
−10
−20
−30
−40
−50
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Potential energy (kT units)
l = s/a
δ=2 nm
δ=0.5 nm
Steric repulsion
δ=2 nm
δ=0.5 nm
Net
Magnetic attraction
Van der Waal attraction

Fig. 4

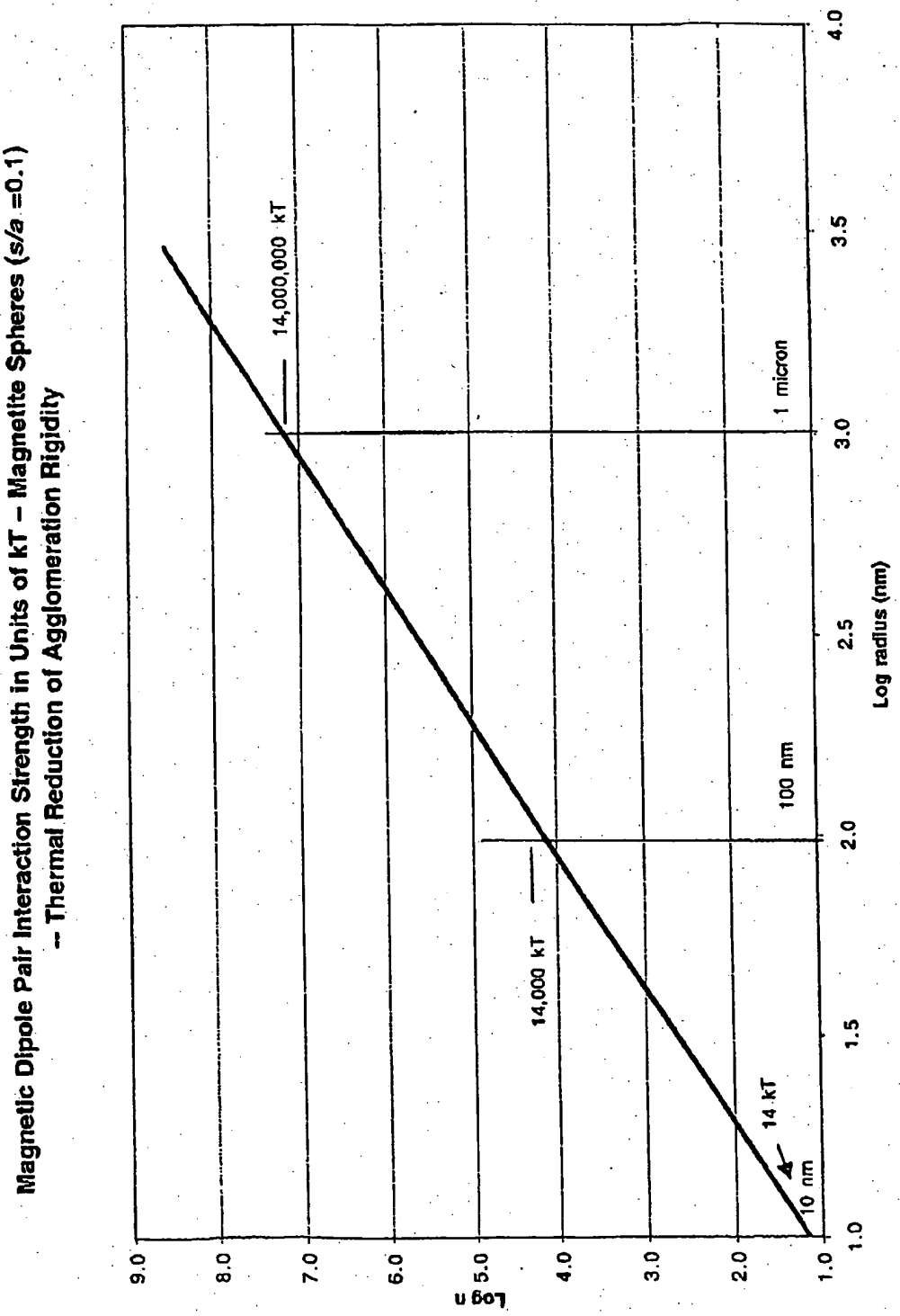
Magnetic Dipole Pair Interaction Strength in Units of kT – Magnetite Spheres (s/a =0.1)
-- Thermal Reduction of Agglomeration Rigidity
14,000,000 kT
14,000 kT
14 kT
1 micron
100 nm
10 nm
Log a
Log radius (nm)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
1.0
1.5
2.0
2.5
3.0
3.5
4.0

Fig. 5

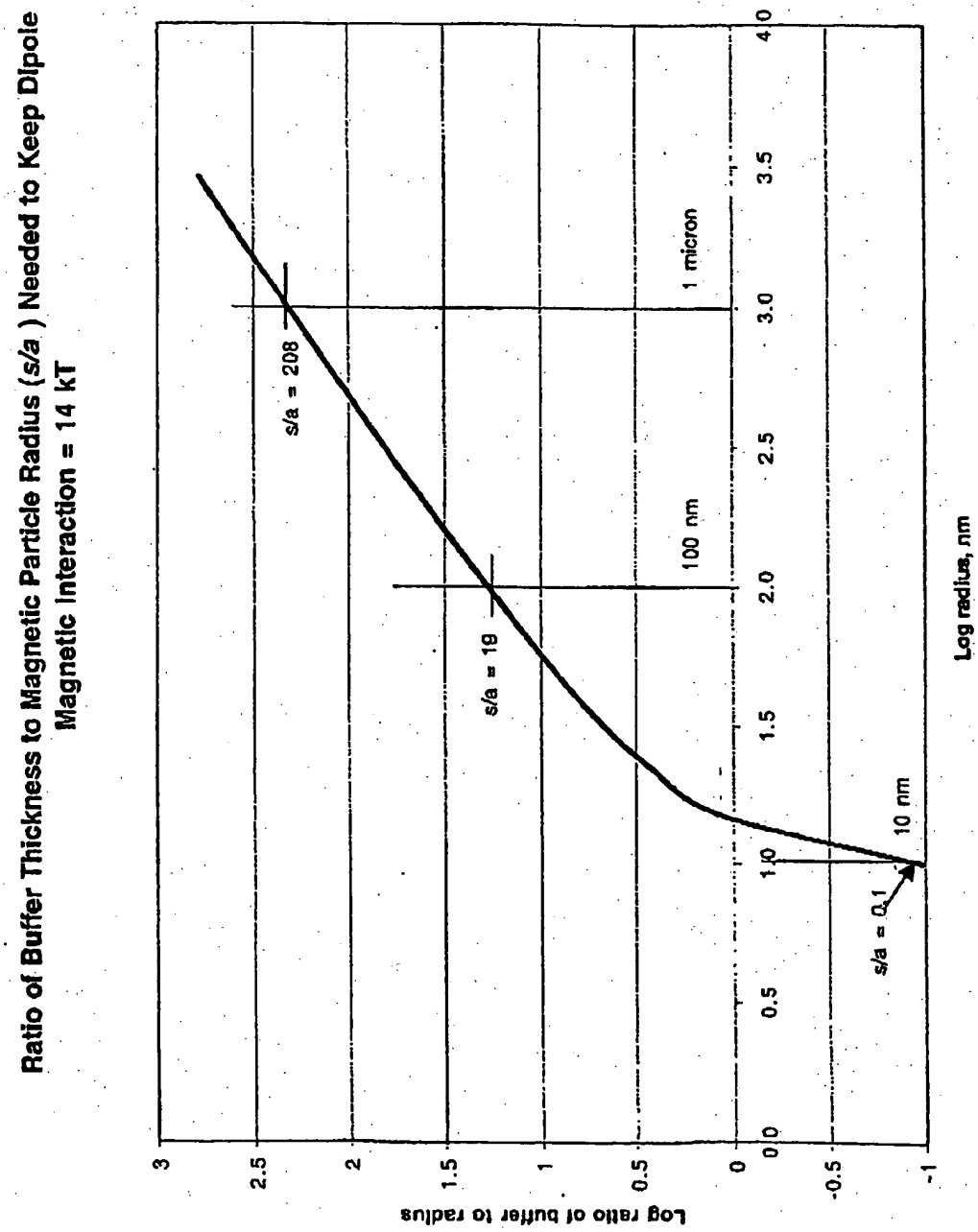
Ratio of Buffer Thickness to Magnetic Particle Radius (s/a) Needed to Keep Dipole Magnetic Interaction = 14 kT
Log ratio of buffer to radius
Log radius, nm
s/a = 208
s/a = 19
s/a = 0.1
1 micron
100 nm
10 nm
3
2.5
2
1.5
1
0.5
0
-0.5
-1
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0

Fig. 6

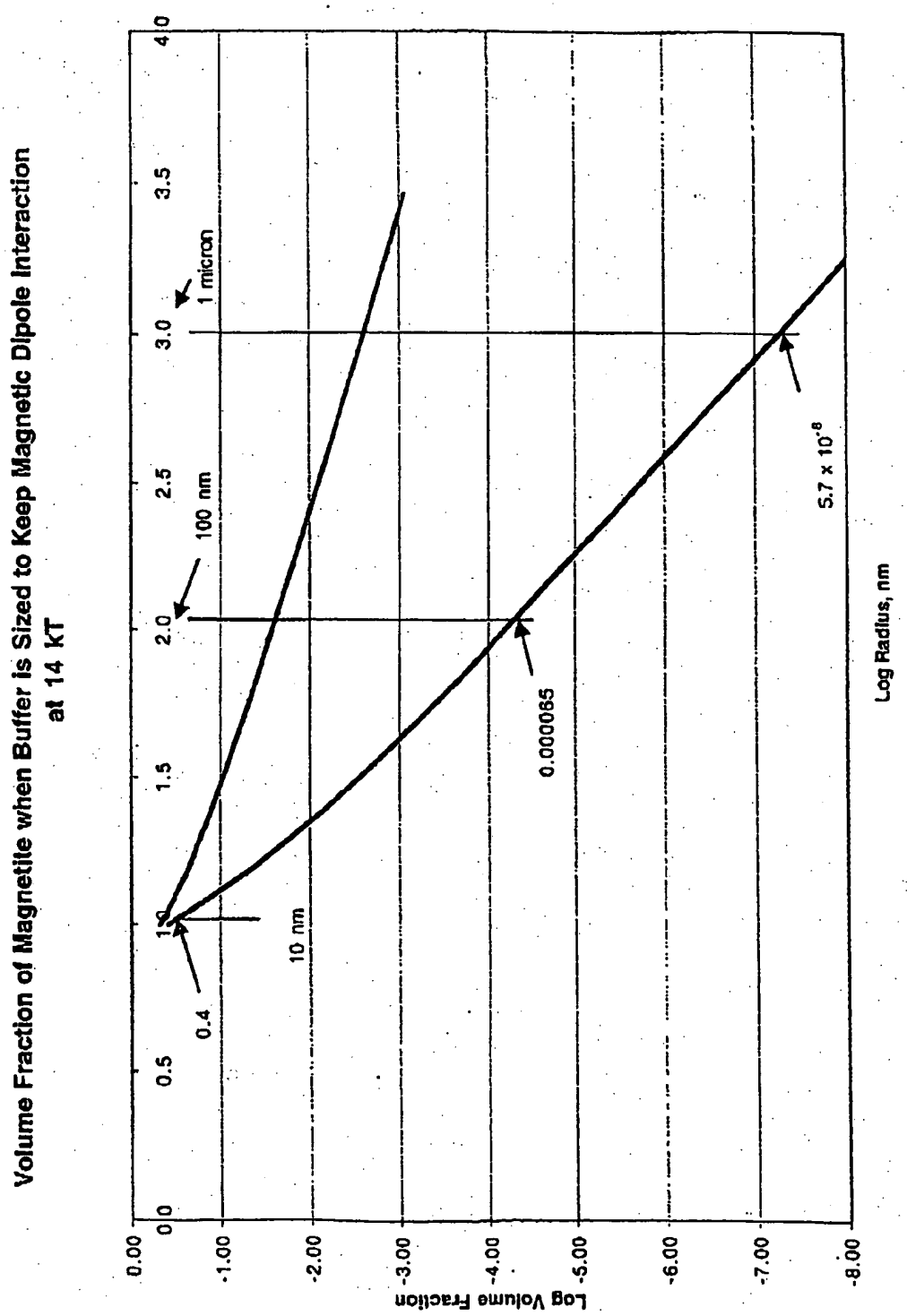
Volume Fraction of Magnetite when Buffer is Sized to Keep Magnetic Dipole Interaction at 14 KT
Log Volume Fraction
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-7.00
-8.00
0
0.5
1.5
2.0
2.5
3.0
3.5
4.0
1 micron
100 nm
10 nm
0.4
0.000085
5.7 x 10⁻⁸
Log Radius, nm

Fig. 7

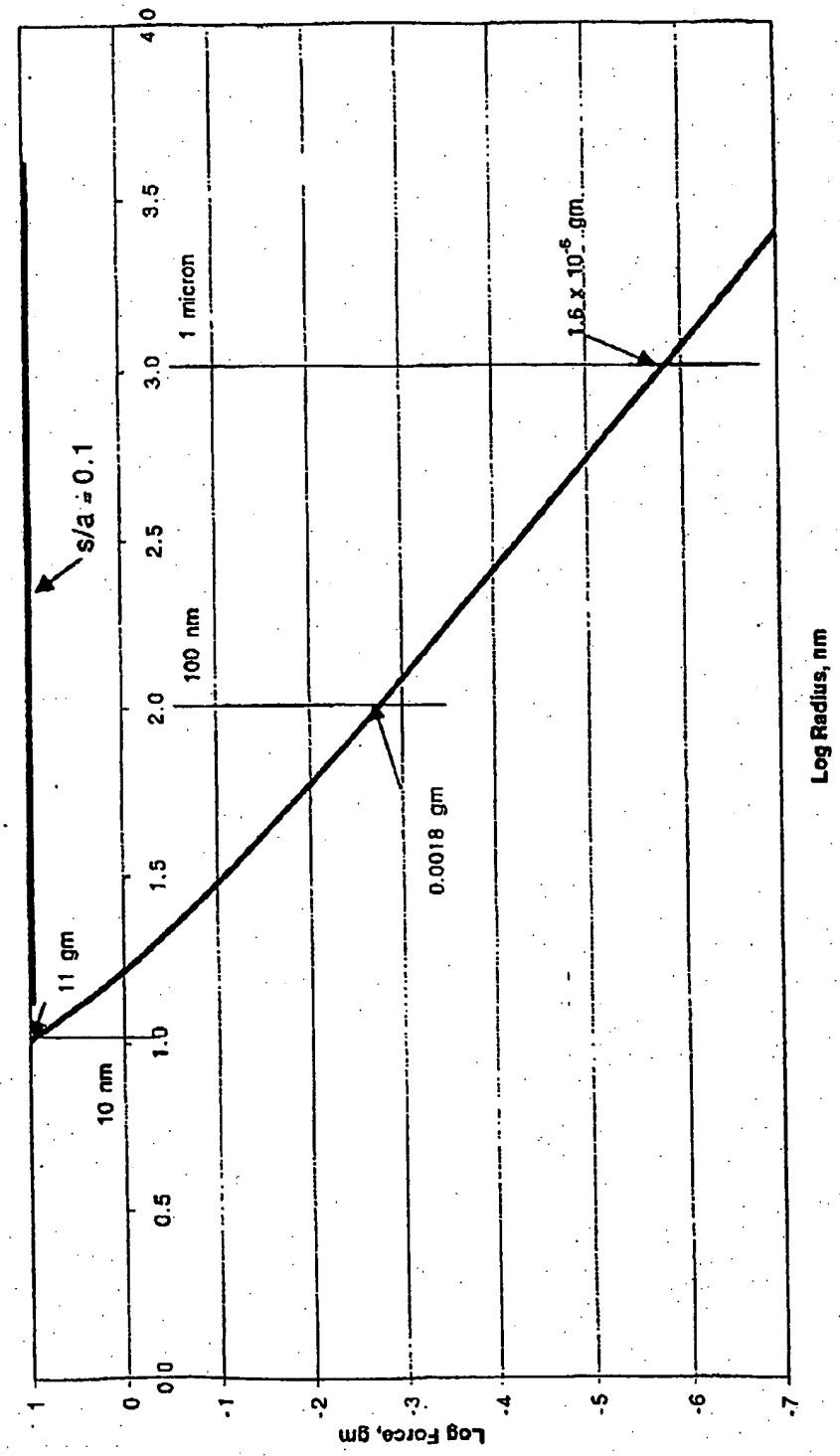
Force on 1 cc of Space- and Magnetic-Saturated, Magnetite for Which the Buffer Thickness is set for 1) Dipole Interaction = 14 kT, or 2) s/a = 0.1; Gradient = 0.7 T/m
s/a = 0.1
11 gm
10 nm
100 nm
1 micron
0.0018 gm
1.6 x 10^-6 gm
Log Force, gm
Log Radius, nm

Fig. 8

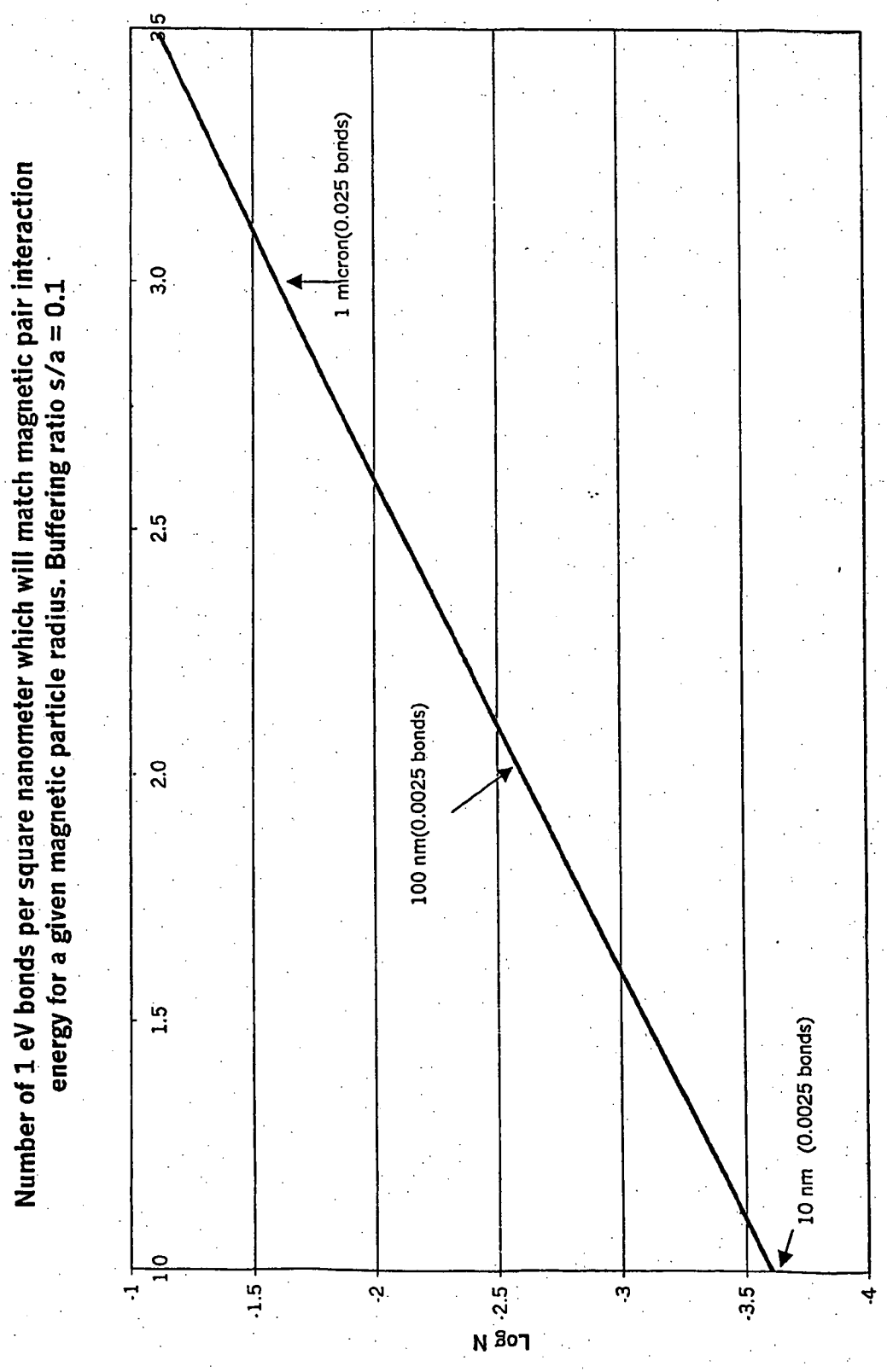
Number of 1 eV bonds per square nanometer which will match magnetic pair interaction energy for a given magnetic particle radius. Buffering ratio s/a = 0.1
1 micron(0.025 bonds)
100 nm(0.0025 bonds)
10 nm (0.0025 bonds)
Log N
Log Radius, nm
-1
-1.5
-2
-2.5
-3
-3.5
-4
1.0
1.5
2.0
2.5
3.0
3.5

Fig. 9

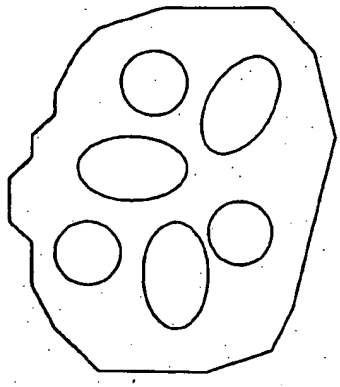

Fig. 10

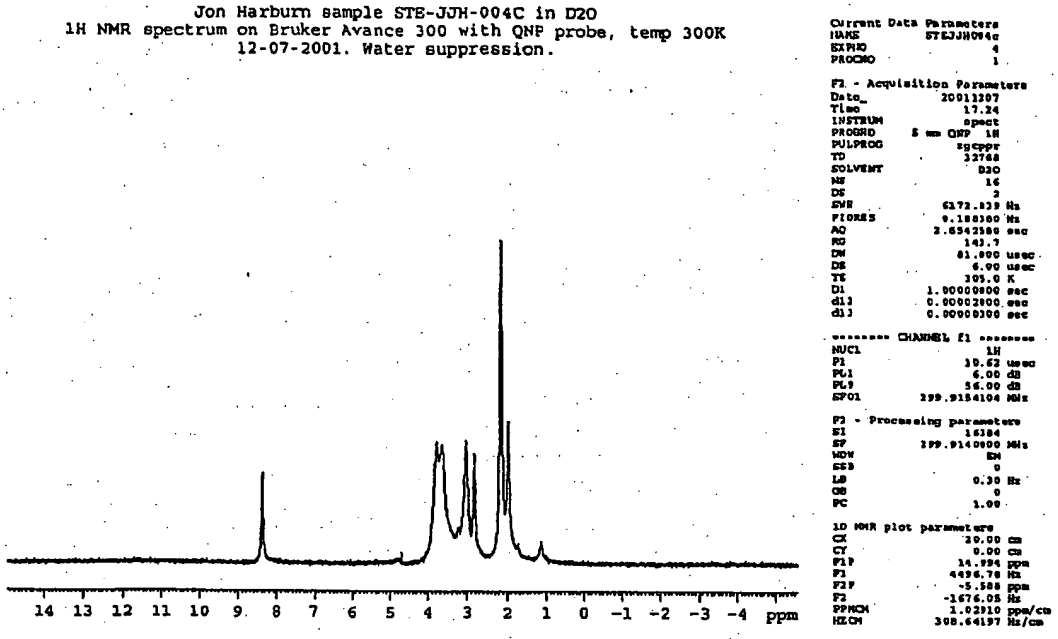
Jon Harburn sample STE-JJH-004C in D2O
1H NMR spectrum on Bruker Avance 300 with QNP probe, temp 300K
12-07-2001. Water suppression.
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 ppm
Current Data Parameters
NAME STEJJH004c
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20011207
Time 17.24
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgcppr
TD 32768
SOLVENT D2O
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188360 Hz
AQ 2.6542580 sec
RG 143.7
DW 81.000 usec
DE 6.00 usec
TE 305.0 K
D1 1.00000800 sec
d11 0.00002800 sec
d12 0.00000200 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.62 usec
PL1 6.00 dB
PL9 56.00 dB
SFO1 299.9154104 MHz
F2 - Processing parameters
SI 16384
SF 299.9140000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 0.00 cm
F1P 14.994 ppm
F1 4496.78 Hz
F2P -5.588 ppm
F2 -1676.05 Hz
PPMCM 1.02910 ppm/cm
HZCM 308.64197 Hz/cm

Fig. 11

Fig. 12

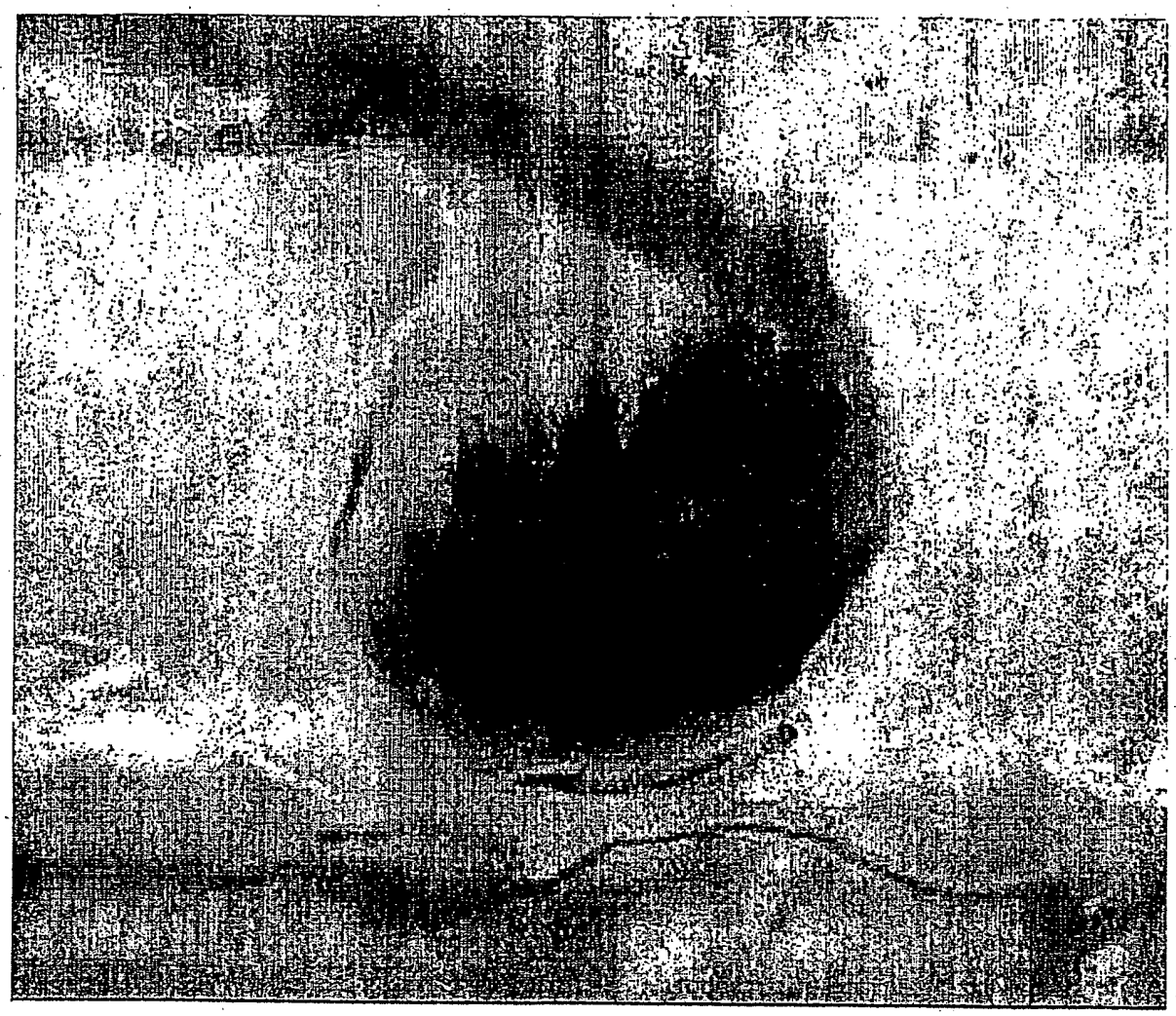

Fig. 13

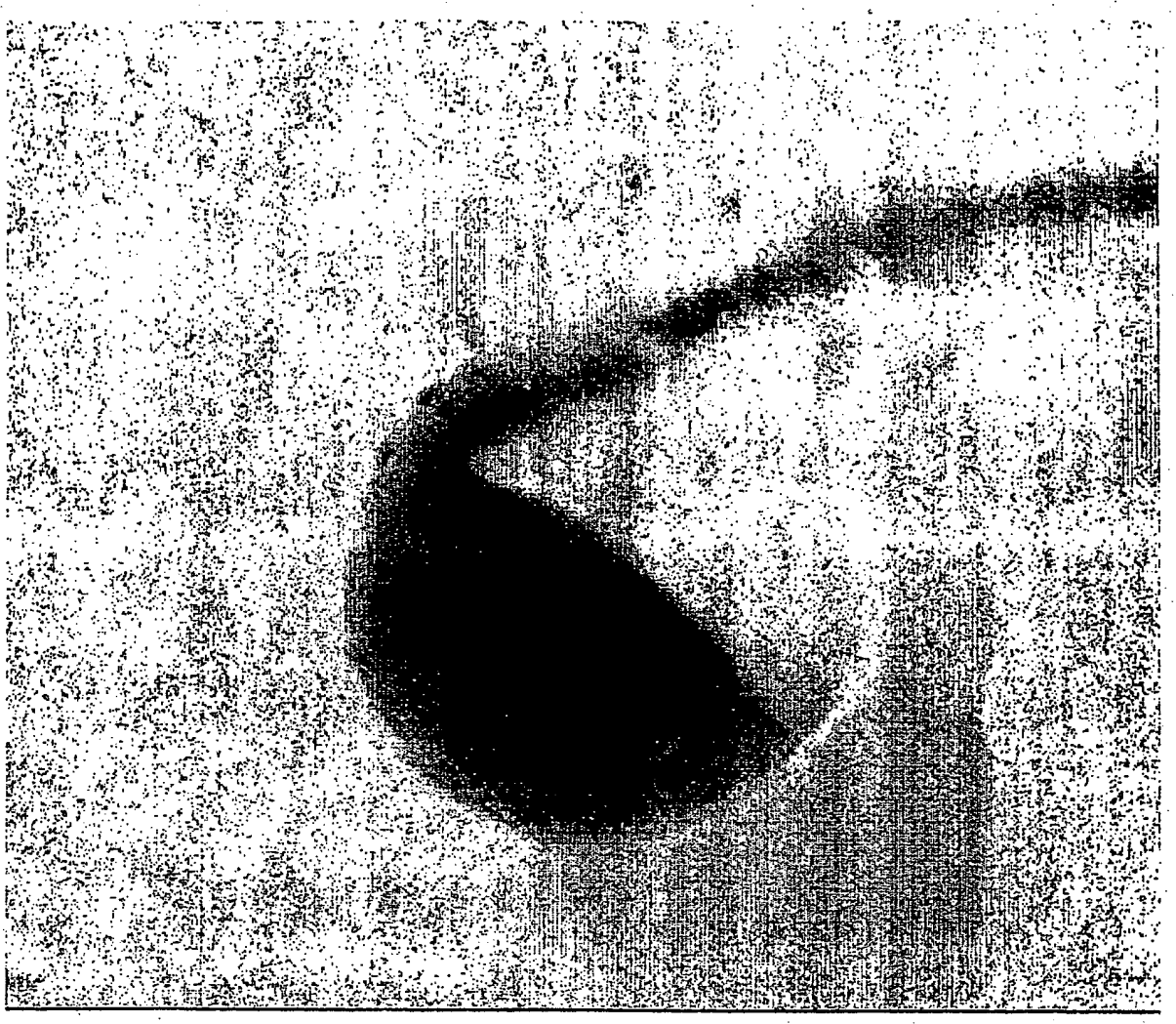

Fig. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/39799

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61M 37/00; A61N 2/00
US CL : 600/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 600/12, 11, 9, 433, 139; 606/32; 424/9; 604/95, 96, 280, 264, 523, 19, 48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 6,355,275 B1 (KLEIN) 12 March 2002 (12.03.2002), See whole document.	1-6,22-25,36,37
Y, P		7,8,10,12,13
A	US 6,355,275 B1 (KLEIN) 12 March 2002 (12.03.2002), see whole document.	11,16-21,26-31
X	US 6,296,604 B1 (GARIBALDI et al) 02 October 2001 (02.10.2001), see whole document.	32,38
Y		7,8,10,12,13
A	US 6,296,604 B1 (GARIBALDI et al) 02 October 2001 (02.10.2001), see whole document.	9,14,15,33-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2003 (10.03.2003)	09 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Brian Szmal Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:
WEST: coated magnetic particles, embolic, embolize, coated iron, cyanoacrylate, coating, adhesive, carrier, covalent bonded coating, x-ray, MRI, contrast agent